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Performing Routine Follow-up Biopsy One Year after Diagnosis Does Not Affect Long-Term Outcomes in Coeliac Disease

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Abbreviations: GSRS Gastro-Intestinal Rating Scale; PGWB Psychological Well-Being Index; SF-36 Short-Form 36

Abstract

Background: A repeat biopsy is recommended, but often omitted in coeliac disease patients on a gluten-free diet. The effect of performing or not performing repeat biopsies is currently unknown.

Aim: To identify factors associated with and the significance of lacking biopsy for long-term outcome. Predictors and the importance of incomplete histological recovery after one year was investigated in re-biopsied patients.

Methods: 760 patients participated in a nationwide follow-up study. Medical data were gathered via interviews and patient records, and blood samples were drawn for serology. Current symptoms and well-being were assessed by validated PGWB, SF-36 and GSRS questionnaires.

Results: Malabsorption was more common among those with a repeat biopsy (46%) than those without repeat biopsy (33%), $p<0.001$, as were severe symptoms at diagnosis (24% vs 16%, $P=0.05$) and concomitant gastrointestinal (40% vs 32%, $P=0.049$) or musculoskeletal (35% vs 27%, $P=0.023$) diseases such as arthritis, osteoporosis and back pain. Repeat biopsy was more rare in subjects diagnosed in private care (11% vs 23%, $P<0.001$) or by screening (10% vs 16%, $P=0.010$). The groups were comparable as to current symptoms and dietary adherence, but those without re-biopsy were less confident of their diet (89% vs 94%, $P=0.002$) and more often seropositive on diet (14% vs 9%, $P=0.012$). They reported better SF-36 physical functioning ($P=0.043$) and less pain and indigestion ($P=0.013$ and $P=0.046$ respectively) and total GSRS ($P=0.052$) score. Incomplete mucosal recovery was predicted by more advanced histological ($P<0.001$) and serological ($P=0.001$) disease at diagnosis, while the groups did not differ in current adherence, symptoms, seropositivity and questionnaire scores.

Conclusion: Severe disease at diagnosis predicted the record of a repeat biopsy and incomplete mucosal recovery. Neither lacking biopsy nor incomplete recovery in a relative short time span of one year was associated with poorer long-term outcome.

Introduction

A careful follow-up of coeliac disease activity after the initial diagnosis is considered important due to the possible complications associated with incomplete healing of the small-bowel mucosa [1, 2]. Owing to the lack of sensitive surrogate markers for histological recovery, most current guidelines recommend a repeat biopsy to be considered on a gluten-free diet [1-6], this often being executed approximately one year after the diagnosis, even if there is lack of evidence on the effect of such practice[3, 7-9]. On the other hand, due to its unpleasantness and resource-consuming nature, the control endoscopy is often omitted in clinical practice, the effect of this on long-term outcomes being currently unknown [7]. Altogether, due to the scarcity of evidence, this topic has been under active discussion in the expert guidelines [1].

Even if a repeat biopsy is conducted, the significance of possible incomplete villous recovery on dietary treatment remains scantly studied. It has been linked, for example, to rare cases of refractory coeliac disease and lymphoproliferative malignancies, but the relevant results appear to be markedly dependent in a fifteen-year follow-up on the study population and the timing of the endoscopy [1,3,8,9,11,12]. We have in fact recently shown that incomplete histological recovery after one year on a gluten-free diet is not associated with reduced short-term well-being or increased risk of cancer and mortality [8]. Further, although after one year's diet up to 50% of coeliac patients may show signs of villous damage, in the long run this is seen in less than 10% of cases and only 0.3% have true refractory coeliac disease [8,10,12].

The rapidly growing number of coeliac disease patients renders optimal targeting and timing of the endoscopic follow-up a major public health issue [8,9,10,12]. To further elucidate these aspects, we investigated factors associated with the omission of routine a invasive follow-up and the value of a repeat biopsy one year after diagnosis with respect to long-term outcome. Simultaneously we were able to further explore the significance of incomplete histological recovery found in the follow-up biopsy in a nationwide coeliac disease cohort.

Materials & Methods

Patients and study design

The nationwide cross-sectional study was conducted in Tampere University Hospital and the University of Tampere. The participants were recruited via newspaper advertisements and with the help of local and national coeliac disease societies. Inclusion criteria were age ≥18 years and a biopsy-proven coeliac disease diagnosis at least two years before the present study. All voluntary participants completed validated questionnaires for current symptoms and health-related quality of life and were interviewed systematically by an experienced physician or study nurse. In addition, blood samples were drawn for serology and medical records reviewed in order to confirm the diagnosis and to complement clinical data and laboratory parameters. Subjects with unclear coeliac disease diagnosis or substantially lacking medical information were excluded. The possible use of olmesartan therapy was also checked for and considered an exclusion criterion, as it may cause severe enteropathy resembling coeliac disease [13].

After collection of study data the results were compared between subgroups of participants who had either undergone (Repeat biopsy) or not (No repeat biopsy) a routine follow-up biopsy approximately one year after the coeliac disease diagnosis. For similar comparison, subjects who had been re-biopsied while on a gluten-free diet were categorized into those with complete and those with incomplete histological recovery after one year on the diet.

The study enrolment and collection of personal information, blood samples and medical data were conducted with the permission and according to the guidelines of the Ethical Committee of the Pirkanmaa Hospital District. All participants gave written informed consent.

Clinical characteristics

The following clinical and demographic data was collected from all participants: gender, age at present and at diagnosis, clinical presentation at diagnosis, the type (gastrointestinal symptoms, extra-intestinal symptoms, screen-detected), duration and severity of symptoms before diagnosis and also their current persistence, family history of coeliac disease, possible symptoms in childhood, presence of coeliac disease-associated and other significant chronic comorbidities, and site (primary, secondary or tertiary care, private care) of coeliac disease diagnosis. Severity of symptoms was further categorized as mild, moderate and severe as previously described in detail [14].

Small-bowel mucosal biopsies

Data on the biopsies were collected from patient records. Our national guidelines recommend at least four small-bowel mucosal biopsies to be taken routinely from each patient upon coeliac disease suspicion and during the repeat endoscopy. The histological specimens are forwarded to the hospitals' pathology department, where the severity of mucosal damage is evaluated in representative biopsy cuttings. In the present study the severity of mucosal lesion was at diagnosis graded into normal, partial, subtotal or total villous atrophy based on the original pathology report. Mucosal recovery on gluten-free diet was defined morphologically based on normalized villous height to crypt depth ratio.

Serology and hemoglobin

The values of serum endomysial antibodies at time of diagnosis, if available, were gathered from patient files. Further serum endomysial antibodies and transglutaminase 2 antibodies were measured in all subjects at the time of the study while on a strict gluten-free diet. Serum IgA-class serum transglutaminase-2 antibodies were tested by commercial enzyme-linked immunosorbent assay (QUANTA Lite h-tTG IgA, INOVA Diagnostics, San Diego, CA). Values >30.0 U/ were rated positive according to the manufacturer's instructions. Serum

endomysial antibodies were assessed by indirect immunofluorescence on human umbilical cord [15] . Serum endomysial antibodies titers 1: ≥5 were considered positive and diluted until negative to 1:50, 1:100, 1:200, 1:500, 1:1000, 1:2000 and 1:4000. The values were further sub-categorized into low (titers 1:5-1:200) and high positive (1:500-1:4000). In cases of selective IgA deficiency the corresponding IgG-class antibodies were measured. Blood hemoglobin values and the possible presence of anemia at coeliac disease diagnosis were gathered from the medical files.

Adherence to the gluten-free diet

Provision of professional dietary advice at coeliac disease diagnosis was verified by patient interview and from the patient records. Current self-reported long-term adherence to the gluten-free diet was inquired and classified as "strict" (minor inadvertent lapses less than a few times a year), "occasional lapses" (lapses less frequently than once per month) and "normal diet" (more frequent lapses) [16,17]. Alongside adherence, also the patient's overall competency to manage the diet and the possible use of purified oats and wheat starch products were asked [18 ,19]. Long-term dietary adherence was further estimated on the basis of coeliac antibody positivity at the time of the present study.

Questionnaires

All questionnaires were filled in at the time of the current study on a long-term gluten-free diet. Short Form 36 Health Survey (SF-36) and Psychological General Well-Being questionnaires (PGWB) were used to assess patients' self-perceived quality of life and gastrointestinal symptoms over time up to the current study. SF-36 comprises of 36 separate questions which can be divided into eight domains as follows; physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due

to emotional problems and mental health [10,20 ,21,22-24] . Items are re-scored from 0 to 100, higher scores indicating better health and quality of life.

PGWB is a well-validated and widely used questionnaire both in general and in coeliac disease [15,16,22,25]. The 22 separate items can be further divided into six sub-dimensions measuring anxiety, depression, well-being, self-control, general health, and vitality. All items use a 6-grade Likert scale with higher scores representing better well-being and quality of life.

Self-perceived severity of gastrointestinal symptoms was evaluated by the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire [15,26] . This comprises of 15 separate items which can be added together as a total score and divided into 5 sub-dimensions measuring abdominal pain, gastro-esophageal reflux, indigestion, diarrhea and constipation. The scoring is based on a 7-grade Likert scale, higher scores reflecting more severe gastrointestinal symptom.

Statistical analysis

Continuous variables and questionnaire findings are presented as medians with quartiles or ranges. Binominal and categorical variables are presented as number of subjects and percentages. Continuous variables were studied using Mann-Whitney test and binominal and classified variables using Chi-square test. A p-value <0.05 was considered significant in all analyses. Statistical analyses were made using the Statistical Package for the Social Sciences version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.)

Results

Altogether 791 participants (median age at diagnosis 44 years, females 78%) had confirmed coeliac disease and were enrolled for further analyses. However, 27 of them were excluded because it was unclear whether they had undergone a repeat biopsy and four due to use of

olmesartan. Of the final cohort of 760 participants 516 (68%) had (Repeat biopsy group) and 244 (32%) had not (No repeat biopsy group) undergone a follow-up endoscopy after a median of one year.

Factors predicting record of a repeat biopsy

Patients with severe clinical or histological presentation or signs of malabsorption at diagnosis were more likely to undergo a repeat biopsy, whereas it was less common among those diagnosed in private care or by screening (Table 1). Record of a histological follow-up was not associated with the duration or type of symptoms and serum endomysial antibodies titers at diagnosis, gender, presence of symptoms during childhood and family history of coeliac disease (Table 1). Median age at diagnosis was also comparable in subjects with and without repeat biopsy (53 vs 55 years, $p = 0.885$)

Long-term follow-up data on patients with and without a repeat biopsy

The median time on a gluten-free diet prior to the current study was eight years. Coeliac disease patients who had undergone a repeat biopsy were more often found to suffer had from concomitant Sjögren's syndrome, musculoskeletal disease or gastrointestinal disease (Table 2). There were no significant differences between the groups in the prevalence of other chronic conditions (Table 2).

Both study groups had received comparable dietary advice at diagnosis and showed equal adherence at time of inquiry (Table 3), but those with no repeat biopsy after one year were less confident as to their current capability to manage a strict diet. Further, the non-biopsied subjects had significantly, even if only modestly, higher serum endomysial antibodies titers on a long-term gluten-free diet. There was, however, no difference between the groups in the presence or severity of current self-estimated symptoms (Table 3), and, based on the GSRS questionnaire, patients without repeat biopsy had even fewer overall gastrointestinal symptoms

and less indigestion (Table 4). There were also no differences between the groups in respect of most current health and quality of life measurements except that subjects without a repeat biopsy reported better SF-36 physical functioning and bodily pain scores (Table 4).

Predictors of incomplete villous recovery in re-biopsied subjects

The result of the re-biopsy was available in 476 (92%) out of the 516 patients undergoing the procedure after one year after diagnosis. Altogether 276 (58%) had reached morphological small-bowel mucosal recovery, while in 200 (42%) it remained incomplete. Factors predicting incomplete recovery were malabsorption (55% vs 41%, $p = 0.003$), high serum endomysial antibodies titer (46% vs 25%, $p < 0.001$) and severe mucosal damage (total atrophy 32% vs 19%, $p < 0.001$) at diagnosis. The recovery and non-recovery groups did not differ in gender, age at diagnosis, family history of coeliac disease, site of diagnosis, severity and duration of symptoms before diagnosis, or presence of symptoms in childhood (data not shown). There was also no difference between the groups in hemoglobin at diagnosis, when analyzed with both genders together, but in separate analysis the median value was lower in women evincing no recovery (12.3 g/dl vs 12.7 g/dl, $p = 0.030$).

Long-term outcomes in re-biopsied patients with and without histological recovery

Coeliac disease patients with incomplete mucosal recovery one year after diagnosis had more concomitant respiratory (15 vs 22%, $p=0.031$) and dermatological diseases (17 vs 10%, $p = 0.043$) at current evaluation, while there was no differences in the frequency of coeliac disease-associated and other chronic diseases. Further, the recovery and non-recovery patients showed similar severity of current gastrointestinal symptoms and quality of life as measured by the questionnaires (data not shown). The groups had also received equally much dietary advice at diagnosis and did not differ in current adherence or capability to manage the diet, in record of

regular follow-up, or in use of purified oats and prevalence of serum transglutaminase-2 antibody positivity (Table 5).

Discussion

The main finding in the present study was that patients with or without endoscopic follow-up did not differ in severity of symptoms or in well-being after a median follow-up time of almost a decade. In addition, the repeat biopsy and no biopsy groups showed excellent and comparable self-reported dietary adherence. Finally, even if a repeat biopsy had been conducted, incomplete mucosal recovery one year after diagnosis did not affect the long-term clinical outcomes.

A repeat biopsy after one year was undertaken especially for patients with severe presentation at diagnosis, while it was more often omitted in screen-detected cases. It would seem logical that, as also seen in other chronic diseases [27], physicians are keener to follow sicker patients with an increased risk of long-term complications. Alternatively, those with milder or screen-detected disease are likely to be less willing to undergo an unpleasant repeat biopsy and, in turn, physicians neglect it in view of to the anticipated better prognosis. This may also explain the similar tendency to omit the repeat biopsy in type 1 diabetes patients, whose coeliac disease is often found by screening and who might have an increased risk of endoscopic complications [28]. Repeat biopsies were also more often taken from patients with concomitant gastro-intestinal and musculoskeletal illnesses, strengthening the conception that those with comorbidities and ongoing symptoms undergo the procedure with a lower threshold.

We also found patients diagnosed in the private sector to have the repeat biopsy omitted more often than those followed in public healthcare. This might be because in private care patients have to pay for the second endoscopy themselves. In addition, in Finland healthcare has evolved around a strong public sector which, as also seen in the present study, treats most coeliac disease patients. In contrast, the private sector is more focused on frontline screening and refers the putative patients to public healthcare for further diagnosis and follow-

up[30]. The results would very likely differ in countries where a system of private health insurances predominates, as in the USA[29,30]. What is more, we found no differences in the rate of re-biopsy between public healthcare levels. This somewhat unexpected finding might be explained by the organized decentralization of coeliac disease diagnostics and the use of uniform nationwide guidelines at all healthcare levels in Finland [28,31]. In fact, nowadays up to 85% of Finnish coeliac disease patients are diagnosed and followed in primary and secondary care [31].

Interestingly, based on the GSRS, coeliac disease patients with a repeat biopsy after one year also remained more symptomatic during the current long-term follow-up. One reason for this may be the aforementioned higher prevalence of gastrointestinal comorbidities in this group. In addition, we have shown that patients with severe presentation at diagnosis are also more likely to remain symptomatic on a long-term gluten-free diet [34]. Likewise, here those with repeat biopsy had currently more bodily pain and decreased physical functioning, again probably since they have more musculoskeletal comorbidities. In contrast, the groups did not differ in any of the PGWB sub-dimension scores, indicating that the minor differences seen in the prevalence of symptoms and comorbidities have no major effect on self-perceived well-being and quality of life.

Another important finding was that the omission of a repeat biopsy one year after the diagnosis did not affect long-term dietary adherence. This suggests that the invasive follow-up does not play a major role in commitment to the gluten-free diet, at least in Finland, where adherence is generally very good and the additional costs of the diet remain reasonable [2,33,35]. Nevertheless, patients without a repeat biopsy considered their capability to manage their diet lower and were somewhat more often seropositive, indicating that a subgroup of patients might benefit from the endoscopic follow-up [34]. Then again, it might be worthwhile investigating whether the re-biopsy is in fact the main issue here or whether other means of follow-up combined with enhanced dietary counselling would be equally effective [36-39].

We also sought to identify associated factors and the long-term significance of incomplete histological recovery one year after coeliac disease diagnosis in a nationwide cohort. As with the repeat biopsy, incomplete recovery was predicted by more severe disease presentation at diagnosis. Similar associations between advanced disease and incomplete recovery on treatment have previously been observed in smaller studies [3,8,40,41]. Further, we recently showed that more ill patients need a longer time to reach complete mucosal recovery[13]. Hence there still was villous atrophy in as many as 42% of the patients here after one year on gluten-free diet. Notwithstanding the differences in the speed of mucosal recovery, long-term damage is present in only 4-6% of patients, a fraction of what is seen after one year[11,33,42,43]. Moreover, no more than 0.3% have true refractory coeliac disease[31]. It must be emphasized that incomplete recovery is not explained by dietary lapses since, in line with previous findings by the present group[9] and Haere and associates [37], also the majority of those without mucosal healing showed excellent adherence to the gluten-free diet.

Notably, the recovery and non-recovery groups did not differ in the prevalence of malignancies. This was in line with our previous study carried out on a different patient cohort in a tertiary center setting[8] and provides an interesting contribution to discussion of the risk of malignancies and the necessity of a repeat biopsy. In contrast to our results, Lebwohl and colleagues[44] found an increased risk of lymphoproliferative malignancies in patients with persistent villous atrophy, even if this could only be seen in those diagnosed before the year 2000. This controversy might be explained by differences in study design and duration of follow-up and improvements in the diagnostics and management of coeliac disease during the past decades. Since what is involved is a rare complication it is also possible that statistical significance was not reached by chance only.

The only significant long-term difference between subjects with or without histological recovery was the higher prevalence of dermatological and respiratory comorbidity in the latter group. In particular, there was no difference in gastro-intestinal symptoms or

general well-being even in the long run, which is in accord with our previous short-term findings[8] in a tertiary center. This strengthens the conception that slower mucosal recovery does not directly affect the improvement of symptoms and quality of life in patients on a strict gluten-free diet. The reason for poorer recovery among those with concomitant skin and respiratory diseases is unclear and remains a subject for further studies.

Our major strength here was the large number of representative patients diagnosed at different levels of health care. We also succeeded in collecting a wide variety of relevant study parameters, and the use of validated questionnaires increases the reliability and reproducibility of results. A limitation is that evaluation of the repeat biopsies was not centralized [45]. Further, the recruitment of most of the participants through coeliac societies may increase the risk of selection bias. The analysis of in particular serious outcomes such as malignancy according to follow-up histology has also the potential for survival bias, as sampling was not done at the time of the repeat biopsy. Finally, we were not able to compare mortality between the groups, since we did not take a certain pre-defined sample but instead enrolled existing patients. Lack of histological follow-up and incomplete mucosal recovery might be associated with increased mortality [9,38], and more studies are needed to further elucidate this issue.

In conclusion, coeliac disease patients with severe initial presentation were more prone to undergo a repeat biopsy after one year on diet and were also found to lack full mucosal recovery if re-biopsied. However, neither the lack of the re-biopsy nor histological recovery was reflected in long-term clinical outcomes and dietary adherence. Based on these results, performing a routine endoscopy one year after diagnosis is not necessarily an optimal approach. Instead, we propose a more personalized follow-up, wherein the repeat biopsy is conducted later, after 2-5 years and only for a selected group based on age, initial disease severity and response to the gluten-free diet.

AUTHORSHIP

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Author contributions: Henna Pekki: Data analysis, data interpretation, drafting of the manuscript. Kalle Kurppa: Data acquisition, data interpretation, critical revision of the manuscript for important intellectual content. Markku Mäki: Data interpretation, critical revision of the manuscript for important intellectual content. Heini Huhtala: Data analysis, data interpretation, critical revision of the manuscript for important intellectual content. Kaija Laurila: Data interpretation, critical revision of the manuscript for important intellectual content. Tuire Ilus: Data interpretation, critical revision of the manuscript for important intellectual content. Katri Kaukinen: Data interpretation, critical revision of the manuscript for important intellectual content

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Table 1. Clinical, serological and histological characteristics at diagnosis in 760 coeliac disease patients without (No repeat biopsy) or with (Repeat biopsy) a follow-up biopsy done.

	No repeat biopsy n=244		Repeat biopsy n=516		P-value
	n	%	n	%	
Females	181	74	413	80	0.093
Clinical presentation[1]					
Malabsorption	80	33	235	46	**0.001**
Gastrointestinal symptoms	204	84	425	82	0.664
Extraintestinal symptoms[2]	97	40	201	39	0.864
Screen-detected	39	16	49	10	**0.010**
Duration of symptoms before diagnosis					0.571
>5 yr	96	42	209	43	
<5 yr	119	50	245	50	
Severity of symptoms at diagnosis					**0.052**
Severe	40	16	122	24	
Moderate	100	41	216	42	
Mild	91	37	158	31	
No symptoms	13	5	18	4	
Symptoms during childhood	72	28	181	35	0.223
Coeliac disease in family	146	63	329	64	0.790
Endomysial antibody titers at diagnosis					0.461
High 1: >200	36	39	77	35	
Low 1:5-1:200	47	51	107	49	
Negative	10	11	35	16	
Severity of villous atrophy at diagnosis					**<0.001**
Total	42	24	124	26	
Subtotal	58	34	196	42	
Partial	73	42	149	32	
Site of diagnosis					**<0.001**
Primary care	41	17	79	15	
Private care	57	23	58	11	
Secondary care	108	44	250	49	
Tertiary care	38	17	125	24	

[1] Patient can present with more than one symptom

[2]Arthritis, dental enamel defects, dementia, dermatitis herpetiformis, glossitis, aphtous stomatitis, gynecological problems, myopathy, neurologic symptoms, osteoporosis, Sjögren's disease, chronic eczema, IgA nephropathy

Table 2. Presence of coeliac disease-associated or other co-morbidities during long-term follow-up in 760 coeliac disease patients without (No repeat biopsy) or with (Repeat biopsy) a follow-up biopsy done.

	No repeat biopsy n=244		Repeat biopsy n=516		P-value
	n	%	n	%	
Associated diseases					
Sjögren's syndrome	1	0	14	3	**0.033**
Type 1 diabetes	6	3	9	2	0.090
Thyroidal disease	39	16	83	16	0.973
Other conditions					
Musculoskeletal disease [1]	66	27	182	36	**0.023**
Gastroenterological disease [2]	78	32	203	40	**0.049**
Gynecological disease	39	16	103	20	0.198
Neurological disease	29	12	67	13	0.671
Psychiatric disease	11	5	25	5	0.834
Any malignancy	9	4	24	5	0.547
Any fracture	68	28	141	28	0.857
No comorbidities	38	16	58	11	0.079

[1]e.g. arthritis, osteoporosis, back pain
[2]e.g. reflux, lactose intolerance, gastritis

Table 3. Long-term follow-up data on 760 coeliac disease patients without (No repeat biopsy) or with (Repeat biopsy) a control biopsy done while on a gluten-free diet

	No repeat biopsy n=244		Repeat biopsy n=516		P- value
	n	%	n	%	
Received dietary advice	231	95	492	95	0.683
Capable of managing gluten-free diet	216	89	480	94	**0.002**
Strictness of gluten-free diet					0.374
Strict diet	231	96	499	98	
Occasional lapses	9	4	11	2	
Normal gluten intake	0	0	0.0	0	
Endomysial antibody titers on gluten-free diet					**0.012**
High 1: >200	12	5	7	1	
Low 1:5-1:200	20	9	38	7	
Negative 1: <5	189	86	486	92	
transglutaminase-2 antibody positivity on gluten-free diet	39	16	57	11	0.139
Current symptoms					0.268
None	155	78	199	72	
Slight	37	19	70	25	
Serious	5	3	7	4	

Table 4. Gastrointestinal symptoms and quality of life during long-term follow-up in 760 coeliac disease patients with (Repeat biopsy) or without (No repeat biopsy) a follow-up biopsy done.

	No repeat biopsy n=244		Repeat biopsy n=516		P- value
	Median	Quartiles	Median	Quartiles	
GSRS sub-scores					
Total	1.8	1.5-2.5	1.9	1.5-2.6	**0.052**
Indigestion	2.3	1.8-3.2	2.5	1.8-3.0	**0.046**
Diarrhea	1.3	1.0-2.3	1.7	1.0-2.0	0.128
Abdominal pain	1.7	1.3-2.7	2.0	1.3-2.3	0.150
Constipation	1.7	1.0-2.7	1.8	1.0-2.7	0.323
Reflux	1.5	1.0-2.0	1.5	1.0-2.0	0.468
SF-36 sub-scores					
Bodily pain	78	53-90	68	48-90	**0.013**
Physical functioning	95	80-100	90	75-100	**0.043**
Role limitations, emotional	100	67-90	100	67-88	0.127
General health perception	65	45-80	60	45-75	0.196
Role limitations, physical	100	25-100	75	50-100	0.223
Vitality	75	53-85	70	55-80	0.583
Social functioning	90	75-100	88	75-100	0.634
Mental health	84	72-100	80	72-100	0.978
PGWB sub-scores					
Total	107	95-117	106	94-115	0.515
General health	14	10-15	13	11-16	0.147
Well-being	17	15-20	18	15-19	0.745
Vitality	18	16-20	18	15-21	0.746
Anxiety	25	21-27	25	21-27	0.810
Depression	17	15-18	17	15-18	0.941
Self-control	16	14-17	16	13-17	0.958

GSRS, Gastrointestinal Symptom Rating Scale, lower scores indicate fewer gastrointestinal symptoms; PGWB, Psychological General Well-Being, higher scores indicate better well-being; SF-36, Short Form 36, higher scores indicate better social functioning

Table 5. Long-term follow-up characteristics in 476 coeliac disease patients with (Recovery) or without (Atrophy) histological response at follow-up biopsy.

	Atrophy n=200		Recovery n=276		P- value
	n	%	n	%	
Received dietary advice	154	77	215	78	0.683
Capable of managing gluten-free diet	184	92	264	95	0.820
Strictness of gluten-free diet					0.060
Strict	195	97	275	100	
Occasional lapses	5	3	1	0	
Normal gluten use					
Use of oats	162	81	231	82	0.947
Regular follow-up	131	66	198	71	0.426
Transglutaminase-2 antibody positivity	45	23	79	28	0.497
Any malignancy	9	5	14	5	0.762
Fractures	53	27	80	28	0.859